SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZAHRO 50

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Un-Coated Tablet Contains:
Hydrochlothiazide BP....50mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Un-Coated Tablet
White coloured, flat tablets plain on one side and plain on the other.
White scored tablet coded 'GP 4436'

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Hypertension.
- Oedema associated with heart failure.
- Oedema caused by other conditions.

4.2 Posology and method of administration

Posology
The daily dose should preferably be taken in the morning.

Adults
Hypertension
The recommended dose is 12.5–50 mg per day initially. The lowest possible maintenance dose should be used especially as the blood pressure lowering effect is not dose dependent.

Hydrochlorothiazide Orion can be combined with other antihypertensive agents and potentiate the effect of these so the doses should be adjusted accordingly.

Oedema
The recommended dose is 25–50 mg or in severe cases 75–100 mg per day initially. The lowest possible maintenance dose should be used. A satisfactory effect during maintenance therapy can be achieved by intermittent dosing e.g. every two to three days.

Hydrochlorothiazide Orion can be combined with other antihypertensive agents and potentiate the effect of these so the doses should be adjusted accordingly.

Treatment control
Serum creatinine and electrolytes should be followed in renal insufficiency. During long-term treatment with Hydrochlorothiazide Orion it should be ensured that the patient's diet contains an adequate amount of potassium.

Special populations

Elderly
Use the adult doses, although they may be more sensitive to the effects of hydrochlorothiazide and may need lower doses.

Children and adolescents (<18 years)
There is no experience in children and adolescents. Therefore, hydrochlorothiazide should not be administered to children and adolescents.

Patients with renal impairment
Hydrochlorothiazide is contraindicated in patients with severe renal impairment (i.e. creatinine clearance ≤30 ml/min) (see section 4.3).

Patients with hepatic impairment
Hydrochlorothiazide is contraindicated in patients with severe hepatic impairment (see section 4.3). Caution is recommended when hydrochlorothiazide is administered to patients with liver disease (see sections 4.4 and 5.2).

Method of administration
Oral use.

4.3 Contraindications
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1

- hypersensitivity to thiazides or related sulfonamides
- severe hepatic or renal insufficiency
- gout.

4.4 Special warnings and precautions for use

Hypotension and electrolyte/fluid imbalance

Symptomatic hypotension may occur in some patients. This was rarely seen in uncomplicated hypertensive patients, but was more likely in the presence of fluid depletion or electrolyte imbalance. Therefore, periodic determination of serum electrolytes and creatinine should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (including hypokalaemia, hyponatraemia, and hypochloraemic alkalosis).

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. If hypercalcaemia occurs, further diagnostic tests are necessary.

Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out a test for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Hyponatraemia accompanied by neurological symptoms (nausea, weakness, progressive disorientation and apathy) has been seen in isolated cases.

Potassium

As with all thiazide diuretics, the excretion of potassium which is caused by hydrochlorothiazide is dose related. At a dose of 12.5 mg/day, the decrease in serum potassium concentrations is on average
0.36 mmol/l after a period of treatment of 6 months. In the case of long-term treatment, the serum potassium concentration has to be established at the start of the treatment and then after 3–4 weeks. This is then to be monitored every 4–6 months if the potassium balance is not affected by other factors (e.g. vomiting, diarrhoea and changes in renal function).

The monitoring of serum electrolytes is particularly important in elderly people, patients with ascites as a result of cirrhosis of the liver and patients with oedema as a result of nephrotic syndrome.

Concomitant treatment with an oral potassium salt (e.g. KCl) or with a potassium-sparing diuretic can be considered in patients receiving

digitalis, in the case of symptoms of coronary heart disease, in patients receiving high doses of a β-adrenergic agonist and in all cases where plasma concentrations are <3.0 mmol/l.

In all cases of combined treatment, the maintenance or normalisation of the serum potassium must be closely monitored. If hypokalaemia is accompanied by clinical symptoms (e.g. muscle weakness, paresis and changes in ECG), the administration of hydrochlorothiazide must be stopped.

Combined treatment consisting of hydrochlorothiazide and a potassium salt or a potassium-sparing diuretic is to be avoided in the case of patients who are also receiving an ACE inhibitor.

Metabolic effects
Just like other diuretics, hydrochlorothiazide can increase the serum uric acid content, but new episodes of gout are only rarely seen with long-term use.

Hydrochlorothiazide must not be used as the medicine of first choice for the long-term treatment of patients with manifest diabetes mellitus. Just as with all thiazide diuretics, glucose tolerance can change during chronic therapy, with the effect being smaller at lower doses. However, diabetes mellitus only rarely occurs during treatment, certainly in the case of patients in whom there are no other predisposing factors. A worsening of the metabolic situation rarely occurs in the case of diabetics.

Small, sometimes reversible increases in the plasma concentrations of total cholesterol, triglycerides or “low-density lipoprotein” cholesterol have been reported in patients in the course of long-term treatment with thiazides and thiazide-like diuretics. The clinical relevance of these findings is a matter for discussion.

Hydrochlorothiazide is not to be used as the medicine of first choice in the case of patients who are receiving treatment for hypercholesterolaemia (diet combined therapy).

Renal insufficiency
Hydrochlorothiazide is ineffective in patients with renal insufficiency (glomerular filtration rate less than 30 ml/min and/or serum creatinine above 1.8 mg/100 ml). It may cause harm to the patient because it may further decrease glomerular filtration rate. Therefore, Hydrochlorothiazide is not recommended in patients with severe renal impairment (see section 4.3).
Periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. Hepatic insufficiency
Hydrochlorothiazide induces fluctuations in serum electrolyte concentrations that may cause a loss of electrolyte homeostasis and hepatic coma may occur in susceptible patients. Hydrochlorothiazide is not recommended in patients with severe hepatic impairment (see section 4.3). Caution is recommended when hydrochlorothiazide is administered to patients with liver disease.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma
Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry.
Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Other warnings
Orthostatic hypotension can occur, so it is necessary to adjust doses appropriately to the needs of each patient.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

Lupus erythematosus can possibly be exacerbated or activated in the course of treatment with thiazides.

Therapy with hydrochlorothiazide should be stopped in the following cases:
- electrolyte disturbances, which are resistant to therapeutic intervention
- orthostatic hypotension
- hypersensitivity reactions
- severe gastrointestinal disorders
- central nervous disorders
- pancreatitis
- blood disturbances (anemia, leukopenia, thrombocytopenia)
- acute cholecystitis
- vasculitis
- aggravation of a pre-existing myopia
- in patients with serum creatinine greater than 1.8 mg/100 ml and creatinine clearance less than 30 ml/min respectively.

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

The following combinations with Hydrochlorothiazide Orion may require dose adjustments.

Medicinal products associated with potassium loss and hypokalaemia
Simultaneous application of hydrochlorothiazide and medicinal products associated with potassium loss and hypokalaemia, e.g. kaliuretic diuretics (e.g. furosemide), glucocorticoids, ACTH, laxatives, carbenoxolone, amphotericin B, penicillin G sodium, salicylic acid and derivatives may enhance the potassium-depleting effect. The monitoring of potassium level is advised. Use of such combinations requires caution.

Lithium
Concomitant application of hydrochlorothiazide and lithium may lead to diminished lithium elimination and increased cardiotoxic and neurotoxic effects of lithium. Therefore, co-administration of lithium and hydrochlorothiazide should only be allowed under strict medical supervision and should not be recommended. If this

combination proves essential, serum lithium level monitoring is recommended during concomitant use.

Other diuretics, blood pressure lowering drugs, betablockers, nitrates, barbiturates, phenothiazines, tricyclic antidepressives, vasodilators, alcohol
Concomitant application of hydrochlorothiazide and these products may intensify the antihypertensive efficacy of Hydrochlorothiazide

ACE inhibitors (e.g. captopril, enalapril)
When administered concurrently with ACE inhibitors (e.g. captopril, enalapril) severe first-dose hypotension and deterioration of renal function may develop. Treatment with diuretics should therefore be stopped 2–3 days before starting ACE inhibitor therapy to reduce the risk of first-dose hypotension.

Salicylates and other NSAIDs (e.g. indometacin) including selective COX-2 inhibitors
Salicylates and other NSAIDs (e.g. indometacin), including selective COX-2 inhibitors, may diminish antihypertensive and diuretic effects of hydrochlorothiazide.

During simultaneous application of NSAIDs acute renal failure may occur in those patients, who develop hypovolaemia during hydrochlorothiazide therapy. Clinical observations suggest that the risk of hospitalization is doubled in patients treated with NSAIDs and diuretics compared with those who only received diuretics. There are single cases of worsening of renal function, especially in patients with poor pre-existing renal function.

Hydrochlorothiazide may intensify the toxic effects of salicylates on the central nervous system.

Cardiac glycosides
If hypokalaemia or hypomagnesaemia occur as an undesirable effect during treatment with diuretics, cardiac arrhythmias can occur in patients who are also treated with digitalis glycosides. It is recommended to monitor electrolytes and correct any imbalance.

Antidiabetic medicinal products (oral agents or insulin)

Thiazide diuretics reduce insulin sensitivity, increasing glucose intolerance and hyperglycaemia. For this reason, hydrochlorothiazide displays interactions with all antidiabetic agents, whether oral or insulin-based, with a corresponding loss of diabetes control. Diabetic patients who begin a treatment with hydrochlorothiazide should therefore monitor their blood glucose levels. It can be necessary to adjust the dose of insulin or oral antidiabetic.

Metformin
Metformin should be used with caution owing to the risk of lactic acidosis induced by possible functional renal failure associated with hydrochlorothiazide.

Allopurinol
Concomitant administration of thiazide diuretics can increase the risk of hypersensitivity reactions to allopurinol.

Amantadine
Concomitant administration of thiazide diuretics can increase the risk of undesirable effects of amantadine by decreasing its tubular secretion.

Cytostatics (e.g. cyclophosphamide and methotrexate)
Concomitant administration of thiazide diuretics can reduce the renal excretion of cytostatics and increase the myelosuppressive effects.

Skeletal muscle relaxants of the curare-type
Effects of skeletal muscle relaxants of the curare-type were increased and prolonged. In cases in which hydrochlorothiazide cannot be stopped before application of curare-type skeletal muscle relaxants, the anaesthetist must be informed.

Anticholinergics (e.g. atropine and biperiden)
The bioavailability of thiazide-like diuretics can be increased by anticholinergics, which is apparent as a result of a reduction in gastrointestinal motility and gastric emptying speed.

Cholestyramine and cholestipol resins
The absorption of thiazide diuretics is reduced by cholestyramine. A reduction in the pharmacological effect can be expected. Cholestipol can delay or reduce the absorption of concomitantly administered hydrochlorothiazide as it can display a strong affinity for anions other than bile acids. If these treatments must be given concomitantly with hydrochlorothiazide they should be given with a time difference of several hours.

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when

hydrochlorothiazide is administered with agents affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics) and the following torsades de pointes-inducing substances (which include some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes:

- Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- Other agents e.g. bepridil, cisapride, diphemanil, erythomycin IV, halofantrin, mizolastine, pentamidine, sparfloxacin, terfenadine, vincamine IV.

Carbamazepine
Co-administration of hydrochlorothiazide with carbamazepine may decrease serum sodium levels. Therefore, serum sodium levels should be monitored.

Chinidin

The clearance of chinidin can be reduced when hydrochlorothiazide and chinidin are given concomitantly.

Tetracyclines
The concomitant administration of hydrochlorothiazide and tetracyclines may cause an increase in serum urea.

Vitamin D
Co-administration of thiazide with vitamin D supplements may increase serum calcium levels due to decreased excretion of calcium.

Cyclosporine
Concomitant treatment with diuretics can increase the risk of hyperuricaemia and gout-like complications.

Calcium salts
Concomitant use of thiazide-like diuretics can result in hypercalcaemia as there is an increase in tubular calcium reabsorption due to decreased urinary excretion.

Betablockers and diazoxide
Thiazide diuretics can increase the hyperglycaemic effect of diazoxide and betablockers.

Methyldopa
In the literature, the occurrence of haemolytic anaemia has been reported with the concomitant use of hydrochlorothiazide and

methyldopa.

Selective serotonin reuptake inhibitors
There is an increased risk of hyponatremia in concomitant therapy with SSRI's and diuretics such as thiazides and furosemide.

4.6 Fertility, pregnancy and lactation
Pregnancy
There is limited experience with the use of hydrochlorothiazide during pregnancy, particularly during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects such as icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia, due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in the rare situations where no other treatment could be used.

Lactation
Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the production of milk. The use of Hydrochlorothiazide during lactation is not recommended. If Hydrochlorothiazide is used during breast feeding, doses should be kept as low as possible.

Fertility
There are no human data regarding the effect of hydrochlorothiazide on fertility. In animal studies hydrochlorothiazide didn't indicate harmful effects on fertility or reproduction (see section 5.3).

4.7 Effects on ability to drive and use machines
Particularly at the start of the treatment, hydrochlorothiazide has minor or moderate influence on the ability to drive and use machines. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or drowsiness may occur.

4.8 Undesirable effects

The adverse events below are classified where appropriate by system organ class and frequency according to the following convention:

Very common:≥1/10
Common: ≥1/100 to <1/10 Uncommon: ≥1/1,000 to <1/100 Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000
Not known: cannot be estimated from the available data

<u>The following adverse events may occur due to disturbances in the electrolyte and fluid imbalance:</u>

During long-term continuous therapy electrolyte- and fluid imbalance is commonly reported, especially hypokalaemia, hyponatraemia, in above hypomagnesaemia, hypochloraemia and hypercalcaemia may develop.

In higher doses loss of fluid and sodium due to enhanced diuresis may occur which may uncommonly provoke symptoms such as dry mouth, thirst, weakness, dizziness, muscle pain and muscle cramps (e.g. calf cramps), headache, nervousness, palpitations, hypotension and orthostatic hypotension.

Excessive diuresis may lead to dehydration and hypovolaemia resulting in haemoconcentration and in rare cases resulting in convulsions, lethargy, confusion, collapse and acute renal failure. In elderly patients or in patients with venous diseases haemoconcentration may provoke thrombosis or embolism.

Hypokalaemia may result in fatigue, sleepiness, muscle weakness, paraesthesia, paresis, apathy, adynamia of smooth muscles with obstipation and meteorism or arrhythmias. Severe potassium loss may result in subileus or paralytic ileus or unconsciousness and coma.

ECG disturbances and aggravated hypersensitivity of cardiac

glycosides may occur. Commonly hypermagnesuria develops, which only uncommonly results in hypomagnesuria, because magnesium is mobilised from the bones.

Development of metabolic alkalosis or aggravation of metabolic alkalosis may result from electrolyte and fluid loss.

The following adverse events also may occur independent of disturbances in the electrolyte and fluid imbalance:

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Not known: Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma).

Blood and lymphatic system disorders:
Common: Thrombocytopenia (sometimes with purpura)
Uncommon: Leukopenia
Very rare: Agranulocytosis, bone marrow depression, aplastic anaemia, haemolytic anaemia, immune haemolytic anaemia due to formation of antibodies against hydrochlorothiazide during simultaneous application of methyldopa.
Immune system disorders:
Rare: Hypersensitivity reactions.

Metabolism and nutrition disorders:
Very common: disturbances in the electrolyte- and fluid imbalance, especially hypokalaemia, hyponatraemia, hypochloraemia and hypercalcaemia; hyperglycaemia and glucosuria in patients without metabolic problems and those with latent or manifest diabetes mellitus or in patients with hypokalaemia; hyperuricaemia, resulting in acute gout in pre-disposed patients; elevations of serum lipids (cholesterol, triglycerides).
Very rare: Hypochloraemic alkalosis
Not known: aggravation of diabetes in patients with manifest diabetes mellitus, manifestation of a latent diabetes mellitus.

Psychiatric disorders:
Rare: sleep disorders, depression.

Nervous system disorders
Rare: Paraesthesia, headache, dizziness or dullness.

Eye disorders
Uncommon: Visual disorders (e.g. blurred vision, xanthopsia) impaired secretion of tears, aggravation of myopia
Not known: Acute myopia, acute angle-closure glaucoma, choroidal effusion.

Cardiac disorders
Common: palpitations
Uncommon Orthostatic hypotension, especially in patients with

intravascular volume depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics (which can be aggravated by alcohol, anaesthetics or sedatives).
*Rare: A*rrhythmias.

Vascular disorders:
Uncommon: Vasculitis (in single cases necrotizing vasculitis).

Respiratory, thoracic and mediastinal disorders *Uncommon:*
respiratory distress, acute interstitial pneumonia
Very rare: pulmonary oedema with shock, probably due to an allergic reaction.

Gastrointestinal disorders
Common: Loss of appetite, gastrointestinal disorders (e.g. nausea, vomiting, diarrhoea, abdominal cramps and abdominal pain)
Rare: constipation.

Hepato-biliary disorders
Uncommon: Pancreatitis, hyperamylasemia, icterus (intrahepatic cholestasis)
Not known: in patients with pre-existing cholelithiasis, an acute cholestasis may develop, jaundice.

Skin and subcutaneous tissue disorders
Uncommon: allergic skin reactions (e.g. pruritus, erythema, photoallergic exanthema, purpura, urticaria)
Very rare: Angiitis necroticans (vasculitis) and toxic epidermal necrolysis, cutaneous lupus erythematodes, lupus erythematodes--like reactions, reactivation of cutaneous lupus erythematodes.

Renal und urinary disorders:
Very common: glucosuria

Common: reversible elevation of serum creatinine and urea
Uncommon: interstitial nephritis.

Reproductive system and breast disorders *Uncommon:*
Impotence.

General disorders and administration site conditions:
Uncommon: drug fever.

Description of selected adverse reactions
Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms of intoxication
Symptoms which can occur after ingestion are acute fluid loss, gastrointestinal symptoms, polyuria or oliguria, dizziness and impaired consciousness. As a result of severe hypokalemia: muscle weakness, fatigue, concentration disorders, dullness, cardiac arrhythmias, hypotension and coma. As a result of acute hyponatraemia: agitation, headache, pain or cramps, and convulsions.

Treatment of intoxication
Treatment consists of the inducement of vomiting, the repeated administration of activated charcoal and the drinking of large amounts. Gastric lavage, where necessary (only useful shortly after intake). Maintenance of the fluid and electrolyte balance. Potassium suppletion, where necessary. Further symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Low-ceiling diuretics, thiazides – Thiazides, plain – Hydrochlorothiazide,
ATC code: C03AA03.

Thiazide diuretics particularly exert their effect in the distal part of the renal tubule by inhibiting NaCl resorption (by antagonism of the Na^+Cl carrier). The increased amount of Na^+ and water in the ductus colligens (collecting duct) and/or the increased filtration rate results in an increase in the secretion and excretion of K^+ and H^+.

In people with normal renal function, diuresis is already promoted after administration of 12.5 mg of hydrochlorothiazide. The resulting increase in the urinary excretion of sodium and chloride and the relatively small increase in potassium in the urine are dose related. The diuretic and natriuretic effect is noticeable after 1–2 hours following the oral administration of hydrochlorothiazide, reaches its maximum after 4–6 hours and can last for 10–12 hours.

Thiazide-induced diuresis initially results in a decrease in plasma

volume, the cardiac minute volume and systemic blood pressure. The renin-angiotensin-aldosterone system can be activated. The hypotensive effect continues to be maintained with the continuation of the medication, probably as a result of the decrease in peripheral resistance; the cardiac minute volume returns to the original value and the plasma volume remains somewhat lower.

With long-term administration, the antihypertensive effect of hydrochlorothiazide is dose related between 12.5 and 50 mg a day. The maximum hypotensive effect is usually reached at 50 mg a day in most patients. Increasing the dose to above 50 mg/day increases the metabolic complications and is rarely necessary from a therapeutic point of view.

If given as a monotherapy, hydrochlorothiazide appears to produce a good effect in around 40–50% of patients, just like other diuretics. In general, elderly people and black people appear to respond well to diuretics as the primary therapy.

Combined treatment with other antihypertensive agents increases the blood pressure lowering effect. In a large proportion of patients who show an unsatisfactory response to a monotherapy, a further decrease in blood pressure can be achieved in this way.

As thiazide diuretics such as hydrochlorothiazide reduce Ca^{+} excretion, these are used in order to prevent the recurrence of renal calcium oxalate stones in patients with idiopathic normocalcaemic hypercalciuria.

With long-term treatment, users of thiazide diuretics appear to have a significantly higher mineral content in their bones than non-users.

In nephrogenic diabetes insipidus, hydrochlorothiazide reduces the volume of urine and increases the osmolality of the urine.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5)

for the highest cumulative dose (~100,000 mg) (see also section 4.4).

5.2 Pharmacokinetic properties

Absorption

The absorption of hydrochlorothiazide administered as hydrochlorothiazide tablets amounts in total to around 70% of the dose. However, variations in absorption as a result of fasting or the intake of food are of little clinical significance. The absorption of hydrochlorothiazide is reduced in patients who suffer from cardiac decompensation.

In the therapeutic domain, the bioavailability and maximum concentration are directly proportional to the dose. After continuous administration, the pharmacokinetics of hydrochlorothiazide do not change and the average concentration is around 100 ng/ml at a dose of 75 mg a day every day for six weeks.

Distribution

Hydrochlorothiazide accumulates in erythrocytes and reaches a maximum concentration around
4 hours after oral administration. After 10 hours, the concentration in the erythrocytes is around three times higher than in the plasma. Binding to plasma proteins of around 40–70% has been reported and the apparent volume of distribution can be estimated to be 5–6 l/kg.

Hydrochlorothiazide crosses the placenta and, in the umbilical cord, reaches a concentration which approaches the concentration in the plasma of the mother. The medicinal product accumulates in the amniotic fluid, where the concentration can be nineteen times the concentration in the umbilical cord.
Hydrochlorothiazide is excreted in the
maternal milk. Elimination

Hydrochlorothiazide is eliminated from plasma with an elimination half-life of on average 9.5 to
13 hours in the terminal elimination phase. Within 72 hours, 60–80% of an oral dose is excreted in the urine, 95% in an unchanged form and around 4% in the form of the hydrolysate 2-amino-4-chloro-m- benzene disulphonamide (ACBS). Up to 24% of an oral dose is excreted in the faeces and a negligible amount is excreted via bile.

In elderly patients, the “steady-state” concentration of hydrochlorothiazide is elevated and systemic clearance is significantly decreased compared with younger patients. For this reason, it is necessary that the treatment of elderly patients take place under strict supervision.

In patients with renal impairment (creatinine clearance between 30 and around 70 ml/min), the rate of urinary excretion is reduced and a higher maximum plasma concentration and AUC are

observed. The average elimination half-life is twice as long.

Hepatic diseases do not have a significant influence on the pharmacokinetics of hydrochlorothiazide however caution is recommended when hydrochlorothiazide is administered to patients with liver disease.

5.3 Preclinical safety data

Animal subchronic and chronic toxicity studies in dogs and rats revealed no marked results except changes in electrolyte balance. In vitro and in vivo mutagenicity assays for gene and chromosomal mutations showed negative results. Long-term carcinogenicity studies with hydrochlorothiazide in rats and mice showed no relevant elevations of tumor amount in the dosage groups. In animal studies, hydrochlorothiazide crosses the placenta. Animal studies showed no effects on fertility in rats and no teratogenic effects in rats, mice and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate
Magnesium stearate
Starch pregelatinized
Starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

Clear and colourless PVC/Al blisters: 10, 20, 30, 50, 90, 98, and 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Zain Pharma limited
Plot No: 209/13741, Colchester Park,
Go-Down No.1, 2, 3, Off
Mombasa Road, Behind Nice
And Lovely House,
P.O. Box: 100167-00101, Nairobi, Kenya

8. MARKETING AUTHORISATION NUMBER(S)

H2025/CTD11033/21421

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7th July 2025

10. DATE OF REVISION OF THE TEXT

7th July 2025